FORM PTO-1390 (REV 11-98)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER
Filed: March 3, 2000
506.38266X00

U.S. APPLICATION NO. (If known. see 37 CFR 1.5)
09/486823

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP98/03980	04 September 1998 (4.09.98)	05 September 1997 (5.09.97)

TITLE OF INVENTION
THERAPEUTIC AGENT FOR NEURODEGENERATIVE DISORDERS

APPLICANT(S) FOR DO/EO/US
SHIMADA, Junichi; KUROKAWA, Masako; IKEDA, Ken; SUZUKI, Fumio; and KUWANA, Yoshisa

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND or SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(l).
4. [ ] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [X] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [X] A change of power of attorney and/or address letter.
16. [X] Other items or information: International Publication No. WO 99/12546(cover sheet)
    International Search Report W/out Refs.
    PCT Request Form

428 Rec'd PCT/PTO 03 MAR 2000

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) 09/486823	INTERNATIONAL APPLICATION NO. PCT/JP98/03980	ATTORNEY'S DOCKET NUMBER 506.38266X00

17. [X] The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5))

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$970.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$840.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$760.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(l)-(4) **$670.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$96.00**

CALCULATIONS PTO USE ONLY		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 840.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(c)).	$	

CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE		
Total claims	5	-20 =	0	X $18.00	$ 0.00	
Independent claims	1	-3 =	0	X $78.00	$ 0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+$260.00	$ 260.00	
TOTAL OF ABOVE CALCULATIONS =					$ 1,100.00	
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).					$ 0.00	
SUBTOTAL =					$ 1,100.00	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +					$	
TOTAL NATIONAL FEE =					$ 1,100.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +					$ 40.00	
TOTAL FEES ENCLOSED =					$ 1,140.00	
					Amount to be: refunded	$
					charged	$

a. [X] A check in the amount of $ 1,140.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ m the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 01-2135 A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

William I. Solomon
Antonelli, Terry, Stout & Kraus, LLP
1300 North Seventeenth Street Suite 1800
Arlington, VA 22209

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SIGNATURE

William I. Solomon
NAME

28,565
REGISTRATION NUMBER

506.38266X00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): SHIMADA, et al.

Filed: March 3, 2000

For: THERAPEUTIC AGENT FOR NEURODEGENERATIVE DISORDERS

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

March 3, 2000

Sir:

Please amend the above-identified application, prior to examination thereof, as follows:

IN THE SPECIFICATION

Please amend the specification as follows:

Page 7, delete Table 1, at the top of the page, in its entirety, and substitute therefor Table 1 in the enclosed APPENDIX.

Page 7, line 18, delete "Sundstrom" and insert --Sundström--.

Page 10, line 18, delete "Ikeda Rika" and insert --Iuchi--.

Page 11, line 16, delete "10" and insert --9-10-- before "animals".

Page 12, line 13, delete "dd-strain" and insert --ddy-strain--.

REMARKS

Applicants have substituted a new, revised Table 1 for Table 1 of the application papers as originally filed. This revised Table 1 provides proper bonding in Compound Numbers 1-3, for the carbon between the two nitrogens of the left-hand heterocyclic ring in Compound Numbers 1-3. It is respectfully submitted that one of ordinary skill in the art, in reviewing Table 1 of the original application papers on the date of filing the application, would have known that the structural formulas for Compound Numbers 1-3 were in error; and, particularly in light of Compound No. 4, would have known that the structural formulas of Compound Numbers 1-3 of the revised Table 1 are correct. Accordingly, it is respectfully submitted that revised Table 1 does not add new matter to the application.

The remaining amendments to the original specification correct typographical errors therein and/or clarify the description; and would have been clear revisions to one of ordinary skill in the art, particularly in light of the remainder of the specification. Accordingly, it is respectfully submitted that these amendments to the specification clearly doe not add new matter to the application.

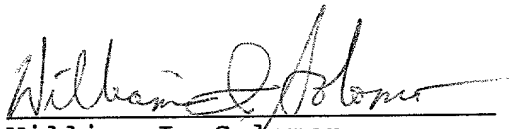
In view of all of the foregoing, entry of the present amendments, and examination of the above-identified

application on the merits in due course, are respectfully requested.

To the extent necessary, Applicants petition for an extension of time under 37 CFR § 1.136. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to the Deposit Account No. 01-2135 (Case No. 506.38266X00) and please credit any excess fees to such Deposit Account.

Respectfully submitted,

ANTONELLI, TERRY, STOUT & KRAUS, LLP



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WIS/slk

SPECIFICATION

THERAPEUTIC AGENT FOR NEURODEGENERATIVE DISORDERS

Field of the Invention

The present invention relates to a therapeutic agent for neurodegenerative disorders.

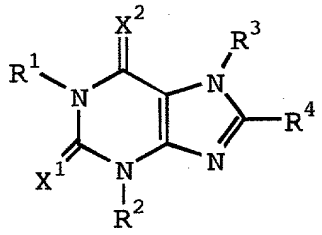
Background of the Invention

Most of the compounds according to the present invention are known compounds, and their adenosine A_2-receptor antagonism, anti-Parkinson's disease action, anti-depressive action, anti-asthmatic action, inhibitory action on bone absorption and action on central excitation are known [Japanese Published Examined Patent Application No. 26516/72, J. Med. Chem., 34, 1431 (1991), J. Med. Chem., 36, 1333 (1993), WO 92/06976, Japanese Published Unexamined Patent Application No. 211856/94, Japanese Published Unexamined Patent Application No. 239862/94, WO 95/23165, Japanese Published Unexamined Patent Application No. 16559/94 and WO 94/01114).

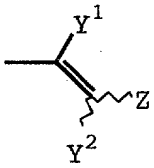
However, it is not known that said compounds have an inhibitory action on neurodegeneration.

Disclosure of the Invention

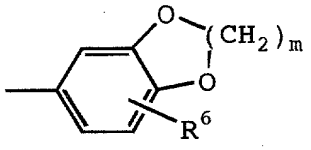
The present invention relates to a therapeutic agent for neurodegenerative disorders, comprising, as an active ingredient, xanthine derivatives represented by formula (I):



wherein R^1, R^2 and R^3 independently represent hydrogen, lower alkyl, lower alkenyl or lower alkynyl; R^4 represents cycloalkyl, $-(CH_2)_n-R^5$ (wherein R^5 represents substituted or unsubstituted aryl, or a substituted or unsubstituted heterocyclic group, and n is an integer of 0 to 4), or the following group:



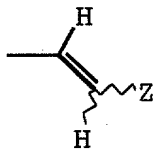
wherein Y^1 and Y^2 independently represent hydrogen, halogen or lower alkyl, and Z represents substituted or unsubstituted aryl, the following group:



(wherein R^6 represents hydrogen, hydroxy, lower alkyl, lower alkoxy, halogen, nitro or amino, and m is an integer of 1 to 3), or a substituted or unsubstituted heterocyclic group; and X^1 and X^2 independently represent O or S, or pharmaceutically acceptable salts thereof.

As the active ingredient for the therapeutic agent for neurodegenerative disorders, preferred compounds are compounds of formula (I) wherein X^1 and X^2 are O, or pharmaceutically acceptable salts thereof; or compounds of

formula (I) wherein R^4 is the following group:



wherein Z has the same meaning as defined above, or pharmaceutically acceptable salts thereof, and specifically preferred compounds are compounds of formula (I) wherein X^1 and X^2 are O and R^4 is the group defined above, or pharmaceutically acceptable salts thereof.

Further, the present invention relates to a method of treating neurodegenerative disorders, which comprises administering an effective dose of a xanthine derivative represented by formula (I) or a pharmaceutically acceptable salt thereof.

Furthermore, the present invention relates to use of a xanthine derivative represented by formula (I) or a pharmaceutically acceptable salt thereof for manufacturing a pharmaceutical composition useful for treatment of neurodegenerative disorders.

Hereinafter, the compound represented by formula (I) is referred to as compound (I).

In the definition of compound (I), the lower alkyl and the lower alkyl moiety in the lower alkoxy mean a straight-chain or branched C_1 to C_6 alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl and hexyl; the lower alkenyl means a straight-chain or branched C_2 to C_6 alkenyl group such as vinyl, allyl, methacryl,

crotyl, 3-butenyl, 2-pentenyl, 4-pentenyl, 2-hexenyl and 5-hexenyl; the lower alkynyl means a straight-chain or branched C_2 to C_6 alkynyl group such as ethynyl, propargyl, 2-butynyl, 3-butynyl, 2-pentynyl, 4-pentynyl, 2-hexynyl, 5-hexynyl and 4-methyl-2-pentynyl; the aryl means phenyl or naphthyl; the cycloalkyl means a C_3 to C_8 cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; examples of the heterocyclic group are furyl, thienyl, pyrrolyl, pyranyl, thiopyranyl, pyridyl, thiazolyl, imidazolyl, pyrimidyl, triazinyl, indolyl, quinolyl, purinyl and benzothiazolyl; and the halogen includes fluorine, chlorine, bromine and iodine. The substituted aryl and the substituted heterocyclic group have 1 to 3 independently-selected substituents such as lower alkyl, hydroxy, substituted or unsubstituted lower alkoxy, halogen, nitro, amino, lower alkylamino, di(lower alkyl)amino, trifluoromethyl, trifluoromethoxy, benzyloxy, phenyl, phenoxy, lower alkanoyl, lower alkanoyloxy, aroyloxy, aralkanoyloxy, carboxy, lower alkoxycarbonyl, lower alkylcarbamoyl, di(lower alkyl)carbamoyl, sulfo, lower alkoxysulfonyl, lower alkylsulfamoyl and di(lower alkyl)sulfamoyl. The lower alkyl and the alkyl moiety of the lower alkoxy, lower alkylamino, di(lower alkyl)amino, lower alkanoyl, lower alkanoyloxy, lower alkoxycarbonyl, lower alkylcarbamoyl, di(lower alkyl)carbamoyl, lower alkoxysulfonyl, lower alkylsulfamoyl and di(lower alkyl)sulfamoyl have the same meaning as the lower alkyl defined above. The halogen has the same meaning as the

halogen defined above. Examples of the substituents for the substituted lower alkoxy are hydroxy, lower alkoxy, halogen, amino, azido, carboxy and lower alkoxycarbonyl. The alkyl moiety of the lower alkoxy and lower alkoxycarbonyl has the same meaning as the lower alkyl defined above, and the halogen has the same meaning as the halogen defined above. The aroyl moiety of the aroyloxy includes benzoyl and naphthoyl. The aralkyl moiety of the aralkanoyloxy includes benzyl and phenethyl.

The pharmaceutically acceptable salts of compound (I) include pharmaceutically acceptable acid addition salts, metal salts, ammonium salts, organic amine addition salts and amino acid addition salts.

The pharmaceutically acceptable acid addition salts of compound (I) include inorganic acid addition salts such as hydrochloride, sulfate and phosphate, and organic acid addition salts such as acetate, maleate, fumarate, tartrate, citrate and methanesulfonate; the pharmaceutically acceptable metal salts include alkali metal salts such as sodium salt and potassium salt, alkaline earth metal salts such as magnesium salt and calcium salt, aluminum salt, and zinc salt; the pharmaceutically acceptable ammonium salts include ammonium and tetramethylammonium; the pharmaceutically acceptable organic amine addition salts include salts with morpholine and piperidine; and the pharmaceutically acceptable amino acid addition salts include salts with lysine, glycine and phenylalanine.

Compound (I) including a novel compound can be produced by the methods disclosed in the above-mentioned publications or according to the methods. The desired compound in the process can be isolated and purified by purification methods conventionally used in synthetic organic chemistry, such as filtration, extraction, washing, drying, concentration, recrystallization and various kinds of chromatography.

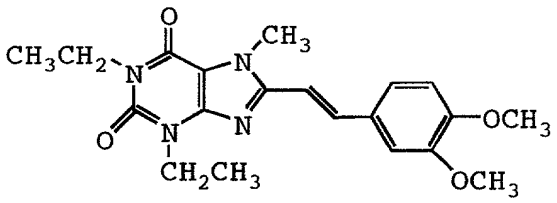
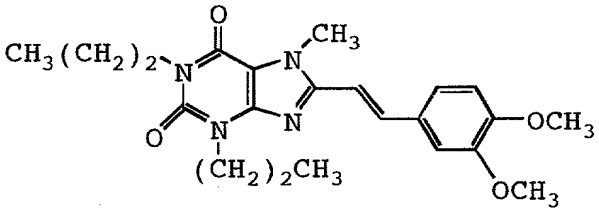
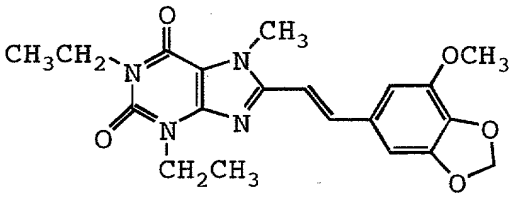
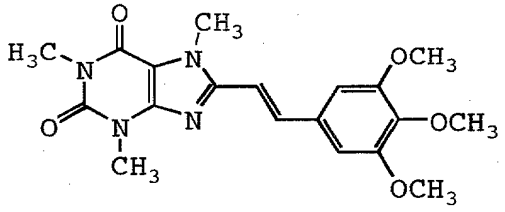
In the case where a salt of compound (I) is desired and it is produced in the form of a desired salt, it may be subjected to purification as such. In the case where compound (I) is produced in the free form and its salt is desired, it is dissolved or suspended in a suitable solvent, and then an acid or a base may be added thereto to form the salt.

Compound (I) and pharmaceutically acceptable salts thereof may be in the form of adducts with water or various solvents, which can satisfactorily be used as the therapeutic agent of the present invention.

Some of compounds (I) have optical isomers, and all potential stereoisomers and mixtures thereof can satisfactorily be used as the therapeutic agent of the present invention.

Examples of compound (I) are shown in Table 1.

Table 1

Compound No.	
1	
2	
3	
4	

Compound 1: (E)-1,3-diethyl-8-(3,4-dimethoxystyryl)-7-methylxanthine (Japanese Published Unexamined Patent Application No. 211856/94)

Melting point: 190.4-191.3 °C

Elemental analysis: $C_{20}H_{24}N_4O_4$

Calcd. (%): C 62.48, H 6.29, N 14.57

Found (%): C 62.52, H 6.53, N 14.56

IR(KBr) νmax(cm^{-1}): 1697, 1655, 1518

NMR($CDCl_3$, 270MHz) δ(ppm): 7.74(1H, d, J=15.5Hz), 7.18(1H, dd,

J=8.3, 1.9Hz), 7.08(1H, d, J=1.9Hz), 6.89(1H, d, J=8.3Hz), 6.77(1H, d, J=15.5Hz), 4.21(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.06(3H, s), 3.96(3H, s), 3.93(3H, s), 1.39(3H, t, J=6.9Hz), 1.27(3H, t, J=6.9Hz)

Compound 2: (E)-8-(3,4-dimethoxystyryl)-1,3-dipropyl-7-methylxanthine (WO 92/06976)

Melting point: 164.8-166.2 °C (Recrystallization from 2-propanol/water)

Elemental analysis: $C_{22}H_{28}N_4O_4$

Calcd. (%): C 64.06, H 6.84, N 13.58

Found (%): C 64.06, H 6.82, N 13.80

IR(KBr) νmax(cm^{-1}): 1692, 1657

NMR(DMSO-d_6, 270MHz) δ(ppm): 7.60(1H, d, J=15.8Hz), 7.04(1H, d, J=2.0Hz), 7.28(1H, dd, J=2.0, 8.4Hz), 7.18(1H, d, J=15.8Hz), 6.99(1H, d, J=8.4Hz), 4.02(3H, s), 3.99(2H, t), 3.90-3.80(2H, m), 3.85(3H, s), 3.80(3H, s), 1.85-1.50(4H, m), 1.00-0.85(6H, m)

Compound 3: (E)-1,3-diethyl-8-(3-methoxy-4,5-methylenedioxy styryl)-7-methylxanthine (Japanese Published Unexamined Patent Application No. 211856/94)

Melting point: 201.5-202.3 °C

Elemental analysis: $C_{20}H_{22}N_4O_5$

Calcd. (%): C 60.29, H 5.57, N 14.06

Found (%): C 60.18, H 5.72, N 13.98

IR(KBr) νmax(cm^{-1}): 1694, 1650, 1543, 1512, 1433

NMR(DMSO-d_6, 270MHz) δ(ppm): 7.58(1H, d, J=15.8Hz), 7.23(1H, d, J=15.8Hz), 7.20(1H, d, J=1.0Hz), 7.09(1H, d, J=1.0Hz), 6.05(2H, s), 4.09-4.02(2H, m), 4.02(3H, s), 3.94-3.89(2H, m), 3.89(3H, s), 1.25(3H, t, J=7.2Hz), 1.13(3H, t, J=6.9Hz)

Compound 4: (E)-8-(3,4,5-trimethoxystyryl)caffeine (Japanese Published Examined Patent Application No. 26516/72)

IR(KBr) νmax(cm^{-1}): 1702, 1667, 1508, 1432

NMR(DMSO-d_6, 270MHz) δ(ppm): 7.61(1H, d, J=16.0Hz), 7.25(1H, d, J=16.0Hz), 7.09(2H, s), 4.03(3H, s), 3.85(6H, s), 3.71(3H, s), 3.45(3H, s), 3.21(3H, s)

MS(EI) 386(M^+)

Hereinafter, the pharmacological activity of compound (I) is shown by the following Test Examples.

Test Example 1: Inhibitory Action on Neurodegeneration

The experiment was conducted according to the method of Sundstrom et al. (Brain. Res. Bulletin, 21, 257-263 (1988)).

In the experiment, 9- to 10-week-old male C57BL/6NCrj mice (supplied by Nippon Charles River) were used. During the period of preliminary breeding, the animals were kept in a laboratory at room temperature (22 to 24 °C) under 50 to 60 % humidity and allowed food and water ad libitum.

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (abbreviated hereinafter as MPTP HCl (RBI Co., Ltd.)) was dissolved at a concentration of 4 mg/ml in physiological saline. A test compound was suspended at a

concentration of 1 mg/ml in 0.3 % dimethyl sulfoxide (DMSO). Each test group consisted of 9 to 10 animals, and a control group was intraperitoneally given physiological saline, and an MPTP HCl administration group and an MPTP HCl + test compound administration group were intraperitoneally given MPTP HCl (40 mg/kg).

After 1 hour, the control group and the MPTP HCl administration group were orally given 0.3 % Tween, and the MPTP HCl + test compound administration group was orally given the test compound (10 mg/kg). After 1 week, the animals were decapitated, and the striatum was removed therefrom under cooling on ice. The striatum was stored in a deep freezer (< -80°C) before a binding experiment.

A [^{3}H]-mazindol binding test was conducted in the following method. A striatum and 300 µl of buffer (120 mM NaCl, 5 mM KCl, 50 mM Tris, pH 7.9) were put into a micro-centrifuge tube and homogenized by portable homogenizer S-203 (manufactured by Ikeda Rika) and centrifuged at 15,000 rpm, 4°C for 5 minutes (by KUBOTA 1710). The precipitates were suspended in 300 µl of buffer and then centrifuged again at 15,000 rpm, 4°C for 5 minutes. The precipitates were suspended in 500 µl of buffer and then distributed into four test tubes in 100 µl portions. The remaining suspension (100 µl) was used for protein quantification. To determine non-specific binding, nomifensine maleate (RBI Co., Ltd.) (final concentration: 10 µM) as an inhibitor of dopamine uptake was added to two test tubes among the four test tubes. The binding reaction was

initiated by adding 25 μl of [^{3}H]-mazindol (final concentration: 10 nM) (Spec. Act. 888 GBq/mmol, a product of NET). The mixture was incubated for 1 hour under cooling on ice, and the striatum homogenate was adsorbed onto a glass filter (Whatman, GF/B) in a cell harvester and washed three times with 5 ml of buffer. The radioactivity on the glass filter was measured with a liquid scintillation counter. For each striatum, specific [^{3}H]-mazindol binding was determined by subtracting the average of non-specific [^{3}H]-mazindol binding from the average of total [^{3}H]-mazindol binding.

Protein quantification was conducted by use of a Bio-Rad DC protein assay kit (Bio-Rad Co., Ltd.) with bovine serum albumin (Sigma Co., Ltd.) as a standard. Specific [^{3}H]-mazindol binding was expressed as the amount of bound [^{3}H]-mazindol per unit weight of protein, and the mean ± standard error was determined for each group (10 animals).

In Table 2, the results are expressed in terms of the amount of specifically bound [^{3}H]-mazindol (fmol/mg protein) in the striatum.

Table 2

Test groups	
Control	1140.3±50.0
MPTP HCl	616.3±32.8###
MPTP HCl + compound 1	950.9±54.1***
Control	1219.3±66.4
MPTP HCl	621.2±27.7###
MPTP HCl + compound 2	784.8±41.6**
MPTP HCl + compound 3	794.9±28.5**
Control	1214.8±46.2
MPTP HCl	674.2±38.1###
MPTP HCl + compound 4	923.5±51.1**

**: $p < 0.01$ (compared with the group given MPTP HCl alone).

***: $p < 0.001$ (compared with the group given MPTP HCl alone).

###: $p < 0.001$ (compared with the control group).

(n = 9 to 10; Wilcoxon rank sum test)

According to the test results, the reduction of the amount of specifically bound [^{3}H]-mazindol by administration of MPTP HCl was inhibited by compound 1. That is, it was revealed that compound 1 exhibits inhibitory action on degeneration of dopaminergic neurons.

Test Example 2: Acute Toxicity Test

Test compounds were orally or intraperitoneally administered to groups of dd-strain male mice weighing 20 ± 1 g, each group consisting of three mice. Seven days after the administration, the mortality was observed to determine a minimum lethal dose (MLD) of each compound.

The MLD value of Compound 1 was greater than 1000 mg/kg for oral administration.

Compound (I) or pharmaceutically acceptable salts thereof have inhibitory action on neurodegeneration and are

useful as a therapeutic agent for neurodegenerative disorders such as Alzheimer's disease, progressive supranuclear palsy, AIDS brain fever, propagating spongy brain fever, Huntington's chorea, multiple sclerosis, amyotrophic lateral sclerosis (ALS), multi-system atrophy, brain ischemia, and attention deficit hyperactivity disorder.

Compound (I) or pharmaceutically acceptable salts thereof can be used as such or in the form of various pharmaceutical compositions. The pharmaceutical compositions of the present invention can be prepared by uniformly mixing an effective amount of compound (I) or a pharmaceutically acceptable salt thereof as an active ingredient with pharmaceutically acceptable carriers. The pharmaceutical compositions are preferably in a unit dosage form suitable for rectal administration, oral or parenteral (including subcutaneous, intravenous and intramuscular administration) administration, etc.

For preparing a pharmaceutical composition for oral administration, any useful pharmaceutically acceptable carriers can be used. For example, liquid preparations for oral administration such as suspension and syrup can be prepared using water; sugars such as sucrose, sorbitol and fructose; glycols such as polyethylene glycol and propylene glycol; oils such as sesame oil, olive oil and soybean oil; preservatives such as a p-hydroxybenzoate; flavors such as strawberry flavor and peppermint, etc. Powder, pills, capsules and tablets can be prepared using excipients such as lactose, glucose, sucrose

and mannitol; disintegrating agents such as starch and sodium alginate; lubricants such as magnesium stearate and talc; binders such as polyvinyl alcohol, hydroxypropyl cellulose and gelatin; surfactants such as fatty acid esters; plasticizers such as glycerin, etc. Tablets and capsules are the most useful oral unit dosage because of the readiness of administration. For preparing tablets and capsules, solid pharmaceutical carriers are used.

Injectable preparations can be prepared using carriers such as distilled water, a salt solution, a glucose solution and a mixture of a salt solution and a glucose solution. The preparation can be prepared in the form of solution, suspension or dispersion according to a conventional method by using a suitable auxiliary.

Compound (I) or a pharmaceutically acceptable salt thereof can be administered orally in the pharmaceutical form described above or parenterally as the injection. The effective dose and administration schedule vary depending on the mode of administration, age, weight, and symptoms of a patient, etc. However, generally, compound (I) or a pharmaceutically acceptable salt thereof is administered in a dose of 1 to 900 mg/60 kg/day, preferably in a dose of 1 to 200 mg/60 kg/day.

Certain embodiments of the present invention are described in the following examples.

EXAMPLE

Example 1: Tablets

Tablets having the following composition were prepared in a conventional manner.

Compound 1 (40 g) was mixed with 286.8 g of lactose and 60 g of potato starch, followed by addition of 120 g of a 10% aqueous solution of hydroxypropyl cellulose. The resultant mixture was kneaded, granulated, and then dried by a conventional method. The granules were refined to give granules used to make tablets. After mixing the granules with 1.2 g of magnesium stearate, the mixture was formed into tablets each containing 20 mg of the active ingredient by using a tablet maker (Model RT-15, Kikusui) having pestles of 8 mm diameter.

The prescription is shown in Table 3.

Table 3

Compound 1	20 mg
Lactose	143.4 mg
Potato Starch	30 mg
Hydroxypropyl Cellulose	6 mg
Magnesium Stearate	0.6 mg
	200 mg

Example 2: Capsules

Capsules having the following composition were prepared in a conventional manner.

Compound 1 (200 g) was mixed with 995 g of Avicel and 5 g of magnesium stearate. The mixture was put in hard capsules

No. 4 each having a capacity of 120 mg by using a capsule filler (Model LZ-64, Zanashi) to give capsules each containing 20 mg of the active ingredient.

The prescription is shown in Table 4.

Table 4

Compound 1	20 mg
Avicel	99.5 mg
Magnesium Stearate	0.5 mg
	120 mg

Example 3: Injections

Injections having the following composition were prepared in a conventional manner.

Compound 1 (1 g) was dissolved in 100 g of purified soybean oil, followed by addition of 12 g of purified egg yolk lecithin and 25 g of glycerin for injection. The resultant mixture was made up to 1,000 ml with distilled water for injection, thoroughly mixed, and emulsified by a conventional method. The resultant dispersion was subjected to aseptic filtration by using 0.2 μm disposable membrane filters, and then aseptically put into glass vials in 2 ml portions to give injections containing 2 mg of the active ingredient per vial.

The prescription is shown in Table 5.

Table 5

Compound 1	2	mg
Purified Soybean Oil	200	mg
Purified Egg Yolk Lecithin	24	mg
Glycerine for Injection	50	mg
Distilled Water for Injection	1.72	ml
	2.00	ml

Example 4: Anal suppository

Formulations for rectal administration having the following composition were prepared in a conventional manner.

Witepsol® H15 (678.8 g, manufactured by Dynamit Nobel, Ltd.) and Witepsol® E75 (290.9 g, manufactured by Dynamit Nobel, Ltd.) were melted at 40 to 50 °C. In the resulting molten mixture were uniformly mixed and dispersed Compound 1 (2.5 g), potassium dihydrogen phosphate (13.6 g) and disodium hydrogen phosphate (14.2 g). The resulting dispersion was poured into plastic suppository molds, and gradually cooled to give anal suppositories containing 2.5 mg of the active ingredient per formulation.

The prescription is shown in Table 6.

Table 6

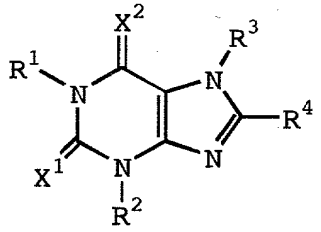
Compound 1	2.5 mg
Witepzol H15	678.8 mg
Witepzol E75	290.9 mg
Potassium dihydrogen phosphate	13.6 mg
Disodium hydrogen phosphate	14.2 mg
	1000 mg

Industrial Applicability

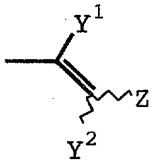
The present invention provides a therapeutic agent for neurodegenerative disorders, comprising a xanthine derivative or a pharmaceutically acceptable salt thereof as an active ingredient.

CLAIMS

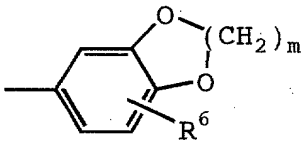
1. A therapeutic agent for neurodegenerative disorders comprising, as an active ingredient, a xanthine derivative represented by formula (I):



wherein R^1, R^2 and R^3 independently represent hydrogen, lower alkyl, lower alkenyl or lower alkynyl; R^4 represents cycloalkyl, $-(CH_2)_n-R^5$ (wherein R^5 represents substituted or unsubstituted aryl, or a substituted or unsubstituted heterocyclic group, and n is an integer of 0 to 4), or the following group:



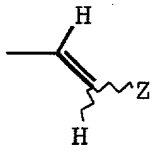
wherein Y^1 and Y^2 independently represent hydrogen, halogen or lower alkyl, and Z represents substituted or unsubstituted aryl or the following group:



(wherein R^6 represents hydrogen, hydroxy, lower alkyl, lower alkoxy, halogen, nitro or amino, and m is an integer of 1 to 3), or a substituted or unsubstituted heterocyclic group; and X^1 and X^2 independently represent O or S, or a pharmaceutically acceptable salt thereof.

2. The therapeutic agent for neurodegenerative disorders according to claim 1 comprising the compound wherein X^1 and X^2 are O, or a pharmaceutically acceptable salt thereof as an active ingredient.

3. The therapeutic agent for neurodegenerative disorders according to claim 1 or 2 comprising, as an active ingredient, the compound wherein R^4 is the following group:



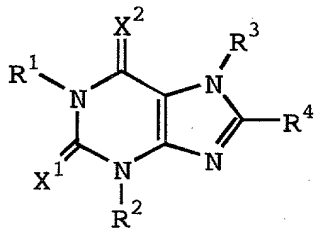
wherein Z has the same meaning as defined above, or a pharmaceutically acceptable salt thereof.

4. A method of treating neurodegenerative disorders, which comprises administering an effective dose of a xanthine derivative according to any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof.

5. Use of a xanthine derivative according to claims 1 to 3 or a pharmaceutically acceptable salt thereof for manufacturing a pharmaceutical composition useful for treatment of neurodegenerative disorders.

Abstract

The present invention relates to a therapeutic agent for neurodegenerative disorders, comprising a xanthine derivative represented by formula (I):



or a pharmaceutically acceptable salt thereof as an active ingredient.

DECLARATION AND POWER OF ATTORNEY FILED WITH U.S. DESIGNATED OFFICE UNDER 35 U.S.C. 371(c)(4)

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name, I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

THERAPEUTIC AGENT FOR NEURODEGENERATIVE DISORDERS

the specification of which was filed as PCT International Application No. PCT/JP98/03980

filed September 4, 1998 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
240565/97 (Number)	Japan (Country)	05 September 1997 (Day/Month/Year Filed)	[X] Yes	[ ] No
(Number)	(Country)	(Day/Month/Year Filed)	[ ] Yes	[ ] No
(Number)	(Country)	(Day/Month/Year Filed)	[ ] Yes	[ ] No
(Number)	(Country)	(Day/Month/Year Filed)	[ ] Yes	[ ] No
(Number)	(Country)	(Day/Month/Year Filed)	[ ] Yes	[ ] No
(Number)	(Country)	(Day/Month/Year Filed)	[ ] Yes	[ ] No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status: patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status: patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status: patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status: patented, pending, abandoned)

(Continued on Page 2)

(11)

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or improsonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00

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Filing Date	March 3, 2000
First Named Inventor	Junichi SHIMADA
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Attorney Docket Number	506.38266X00

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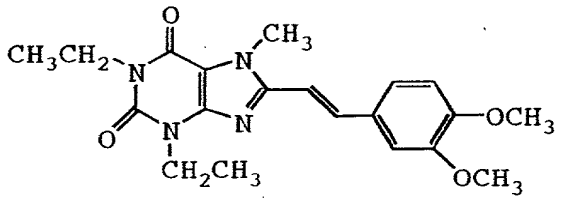
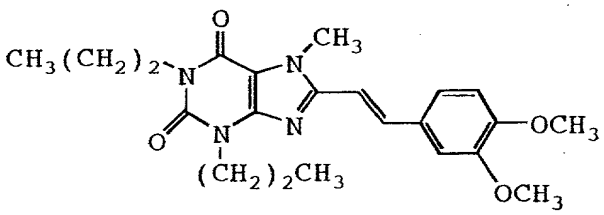
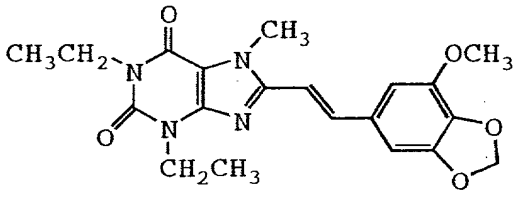
APPENDIX

Table 1

Compound No.	
1	
2	
3	
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